

### A STUDY ON PROGNOSTIC VALUE OF SERUM FERRITIN, SERUM VITAMIN D AND C REACTIVE PROTEIN LEVELS IN PAEDIATRIC SEPSIS

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#### Abstract

**Background:** Sepsis in children is a significant cause of morbidity and mortality worldwide. As biomarkers are present during an infectious insult's response, they can be used for screening, diagnosis, prognosis (risk stratification), therapy response monitoring, antibiotic rationalization and determining the length of stay in the hospital. The aim of this study is to evaluate the levels of serum CRP, serum Ferritin and serum Vitamin D levels at 0 hrs and 48 hrs after admission, and evaluate the relationship between serum CRP and its relevance with serum ferritin and serum vitamin D in paediatric sepsis. This study helps in effective management of paediatric sepsis for paediatricians. **Materials and Methods:** A total 100 Children between age 1 to 12 yrs. with clinically suspected sepsis as per the definition given by the International Pediatric sepsis Consensus Conference were selected. Patients were classified into sepsis with shock (n=30) and sepsis without shock (n=70) and the levels of CRP, ferritin and Vitamin D were estimated at 0 hrs. and 48 hrs. after admission. **Result:** The Mean  $\pm$  SD levels of CRP and ferritin are significantly higher in septic shock, culture-positive patients compared to patients without septic shock and culture-negative patients with significance. The mean  $\pm$  SD values of CRP was lowered 48 hrs after admission compared to at 0 hrs. of admission with a significance. The mean  $\pm$  SD values of ferritin increased after 48 hrs. when compared to 0 hrs. The mean  $\pm$ SD values of Vitamin D did not show any significant difference between septic shock VS without septic shock and culture positive VS culture-negative patients at 0 hrs. Vitamin D levels were significant only at 48 hrs. in patients of septic shock vs without shock. **Conclusion:** Both CRP and ferritin levels have favorable test performance but vitamin D is less reliable.

## INTRODUCTION

Sepsis in children is a significant cause of morbidity and mortality worldwide.<sup>[1]</sup> The mortality rate of sepsis in children from paediatric intensive care unit (PICU) of developing nations is higher than 50%.<sup>[1]</sup> According to World Health Organization statistics, 80% of death in children <4 years can be classified as sepsis-related deaths. The top four causes of childhood mortality are severe pneumonia, severe diarrhoea, severe malaria, and severe measles as reported by the World Health Organization (WHO). Despite various efforts, severe sepsis and septic shock are still considered as the leading cause of infection related death in children.<sup>[2]</sup> The

International Sepsis Consensus Conference in the United States in 2002, defined the clinical criteria of systemic inflammatory response syndrome (SIRS) and sepsis in children and was considered a turning point in clinical detection of sepsis.

Laboratory tests are as important as physiological parameters for the early diagnosis of sepsis. C-reactive protein (CRP) is an acute-phase protein that serves as an early marker of inflammation or infection. The protein is synthesized in the liver and is normally found at concentrations of less than 10 mg/L in the blood. During infectious or inflammatory disease states, CRP levels rise rapidly within the first 6 to 8 hours and peak at levels of up to 350–400 mg/L after 48 hours. When the inflammation or tissue destruction is resolved, CRP levels fall, making it a

useful marker for monitoring disease activity. During last decade measurement of CRP, a good inflammatory marker, has been added to the set of haematological tests (total leukocyte count, neutrophils, and band forms) that have long been used in clinical practice. However it doesn't have specificity to distinguish viral from bacterial infections.<sup>[3,4,5]</sup>

Ferritin is a ubiquitous intracellular iron storage protein composed of 24 light (L) and heavy (H) ferritin monomers.<sup>[5,6]</sup> Serum ferritin, in addition to representing body iron stores, is an acute-phase protein that increases in the presence of circulating inflammatory cytokine such as interleukin-1 and tumor necrosis factor.<sup>[7]</sup> During infection and inflammation, iron is withdrawn from the circulation and is redirected to hepatocytes and macrophages, thereby reducing the availability of this essential nutrient to invading pathogens and is a virulence factor for many microorganisms.<sup>[8]</sup> The resulting iron overload in hepatocytes and macrophages enhances the translation of ferritin through the iron response protein.<sup>[9]</sup> Part of the elevated ferritin load in macrophages may translocate to the lysosomal compartment, where it protects this compartment from reactive iron, followed by ferritin secretion through the secretory-lysosomal pathway. Ferritin may also enter the circulation via the classical ER/Golgi-dependent secretory pathway in hepatocytes.<sup>[5,6]</sup>

Vitamin D potentiates mineralization of bone via its role in the stimulation of calcium absorption in the intestine. Vitamin D is an important mediator in the immune system and its inhibitory role in sepsis pathogenesis has been evaluated. Vitamin D can regulate acquired and innate immune responses. This vitamin prevents overexpression of inflammatory cytokines and is an important mediator in aggregation of leukocytes, formation of local inflammation, and anti-bacterial responses in innate immunity. Vitamin D deficiency has been shown to be associated with sepsis, acute respiratory distress syndrome and acute kidney injury.<sup>[7]</sup> Aim of this study is to evaluate the levels of serum CRP, serum Ferritin and serum Vitamin D levels at 0 hrs and 48 hrs after admission, and evaluate the relationship between serum CRP and its relevance with serum ferritin and serum vitamin D in paediatric sepsis.<sup>[8,9]</sup>

## MATERIALS AND METHODS

A cross-sectional study was performed in the Department of Biochemistry at Niloufer Hospital, Osmania General Hospital, Osmania Medical College, Hyderabad, Telangana from March 2020 to October 2020 for a period of 8 months.

A total of 100 patients were recruited for the study according to the International Sepsis Consensus Conference 2002 definition criteria. They were divided into two groups, sepsis without shock (n=70) and sepsis with shock (n= 30) at Niloufer hospital for

women and children Hyderabad, Telangana. Relevant routine laboratory investigations were carried out.

### Inclusion Criteria

Children between 1 to 12 yrs with suspected sepsis as per the definition of International paediatric sepsis consensus conference 2002.

### Absolute Criteria

Core temperature of  $>38.5^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$ , Leukocyte count elevated or depressed for age, Tachycardia or tachypnoea according to age with culture-proven or suspected infection by clinical examination imaging and laboratory investigations.

### Exclusion Criteria

Paediatric surgical, trauma and burn cases, Children dying within 24hours of PICU admission, Autoimmune diseases, Evidence of malaria, Diagnosis of the hemophagocytic syndrome, Recipient of blood transfusion in the last 4months, and Cases of hepatitis, Children with other causes of shock, not due to sepsis itself, e.g. Cardiogenic, anaphylactic etc. and Children with known malignancies and immunosuppressive treatment.

### Specimen Collection

4ml of venous blood was drawn under aseptic conditions, into serum vacutainers with a clot activator. Samples were allowed to clot and then centrifuged. The serum was separated and stored in Eppendorf tubes at  $-20^{\circ}\text{C}$ . Approval was taken from the hospital ethics committee and written consent was obtained from parents

### Parameters Estimated

Measurements of serum CRP, serum ferritin, and serum Vitamin D levels after diagnosis of sepsis and 48 hrs after the first sample was carried out. This is to know the difference observed in the values at the time of admission and after 48 hrs of admission by which time treatment would have been started. To know the difference in the 2 groups paired t-test and unpaired t-test was performed. ROC analysis was done with Area under the curve to know the diagnostic accuracy of the parameter measured. The significance of the difference between the means was expressed as a p-value and a p-value of less than 0.05 was considered statistically significant. Pearsons correlation was done for comparison between CRP and ferritin, CRP and Vitamin D and between Vitamin D and ferritin at 0 hrs and after 48 hrs.

Serum CRP was measured by latex turbidimetry method by measurement of antigen-antibody reaction by endpoint method by Beckman coulter 5800Au. Serum ferritin and serum vitamin D were measured by the Chemiluminescence immunoassay (CLIA) method in Siemens Advia Centaur XPT.

**Following data was collected from the eligible enrolled patients:** Age, Gender, Length of stay in the

hospital, serum CRP, serum Ferritin and serum vitamin D at 0 hrs and after 48 hrs after admission. The data was analyzed using statistical package for social sciences (SPSS) version 20 and the results were expressed as Mean and Standard deviation of various parameters in different groups. The significance of the difference between means was calculated by paired and un-paired T-tests, ROC curves analysis and by correlation coefficients expressed as P-value and a P-value of <0.05 was considered as statistically significant. The results were expressed in milligrams /liter for Serum CRP (mg /L). For serum Ferritin and Serum vitamin D in nano grams /deciliter (ng/dL).

## RESULTS

This study included 100 children. All were selected on the basis of sepsis definition defined by the International pediatric sepsis consensus conference., They were divided into two groups sepsis with shock and sepsis without shock. Among 100 children 41 were culture positive and 59 were culture negative. In this study infection was proven by positive body fluid cultures in 41% of the study group, 25% were positive blood cultures, and 11% urine cultures were positive. CSF and stool culture was positive in 4% and 1% of cases respectively. Others had positive findings on clinical examination, imaging and laboratory tests. In this study, the source of sepsis was pneumonia, bacterial meningitis, urinary tract infection etc. [Figure 1] shows fever with increased respiratory rate by more than 2SD above normal for age values was found in 49% of the study group. Fever with tachycardia at least 2 SD above normal for age values was noted in 72 %, while 37% of the study group had fever and abnormal count of leukocytes. Hypothermia was not noted. [Figure 1] Mean age is 6.08±3.37. Maximum age group is between 5-12yrs constituting 55% of the cases followed by 2-5 yrs constituting of 28% and 18% are between 1-2 yrs. In the study group taken 57% are males and 43% are females.

The mean length of stay in hospital for sepsis without shock patients were 7.57 days whereas the mean length of stay in hospital for sepsis with shock patients were 12.48 days showing no significant difference in the age and gender between the Sepsis with shock group and Sepsis without shock group. There was a statistically significant difference in the duration of illness. [Table 1]

Mean CRP level which are significantly higher in a culture-positive group (71.93 ± 24.21) compared to the culture-negative group (45.92 ± 24.88) at admission (p-0.000) and 48 hrs after admission (p-0.013). Mean ferritin levels in culture positive patients and culture negative are 983.1 ± 596.7 and 495.3 ± 452.1 at 0 hrs with p value 0.000 showing significance. At 48 hrs after admission in culture positive patient showed mean ferritin value of 1299.3 ± 905.4 and culture negative patients showed 462.3 ± 437.5 with significant p-value of 0.016. when comparison of Vitamin D levels was done by unpaired T-test and between culture-positive and culture-negative groups at 0 hrs and 48 hrs after admission p-value was 0.334 and 0.766 respectively which was not statistically significant. [Table 2]

Mean CRP value in sepsis with shock and sepsis without shock was 80.47 ± 14.04 and 46.34 ± 25.69 respectively at 0 hrs of admission and 48 hrs after admission in sepsis with shock and sepsis without shock was 39.16± 21.0 and 22.78 ±14.8 respectively with p value 0.00 which is statistically significant. Mean ferritin values of sepsis with shock group at 0 hrs (1418 ± 282.0) were significantly higher compared to sepsis without shock group (385.4 ± 333.5) ((p- 0.000). At 48 hrs mean ferritin values are 1539.4 ± 1492.9 and 490.9 ± 327.5 in sepsis with shock and sepsis without shock respectively with p value <0.05 which is significant as shown in table 3. The vitamin D levels at 0 hrs in sepsis with shock and without shock are 14.08 ± 6.79 and 14.56±6.5. P-value is 0.74 with no significance. The vitamin D levels at 48 hrs. in sepsis with shock and without shock are 11.90 ± 7.1 and 15.20±7.1 respectively and P-value is 0.043 is significant. [Table 3]

**Table 1: Comparison Of Demographic Data Of The Study Group.**

| Demographical Data                           | Sepsis with shock           | Sepsis without shock       | p-value   |
|--|-----------------------------|----------------------------|-----------|
| Age (mean, minimal -maximal)                 | 5.6 yrs. (1yr – 10yrs)      | 6.29 yrs. (1yr – 12yrs)    | 0.35 (NS) |
| Gender girls/boys (number)                   | 19/11                       | 24/46                      | 0.07 (NS) |
| Duration of illness mean, (minimal -maximal) | 12.17 days (2 days-39 days) | 7.57 days (2 days-35 days) | 0.03 (S)  |

**Table 2: Comparison of mean CRP, Ferritin, Vitamin- D levels between culture-positive and culture-negative group**

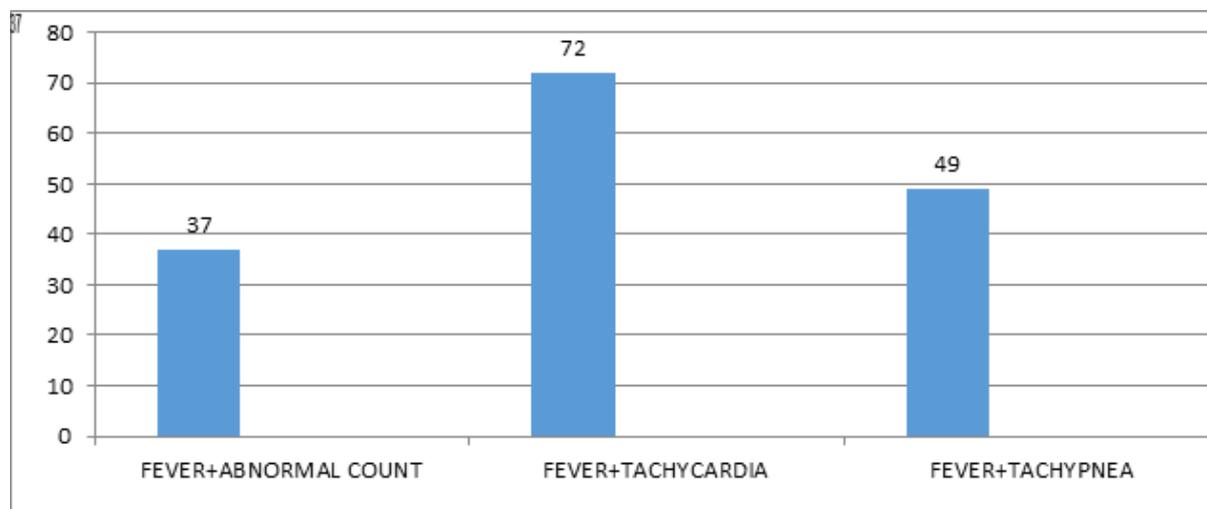
| Parameters | Culture positive/negative | 0hrs (SD) mg/l | P value | 48hrs (95%CI)mg/l | P – value |
|------------|---------------------------|----------------|---------|-------------------|-----------|
| CRP        | Culture positive          | 71.93 (24.21)  | 0.000   | 35.53(21.18)      | 0.013     |
|            | Culture negative          | 45.92(24.88)   |         | 23.64(15.22)      |           |
| Ferritin   | Culture positive          | 983.1 (596.7)  | 0.000   | 1299.3 (905.4)    | 0.016     |
|            | Culture negative          | 495.3 (452.1)  |         | 462.3 (437.5)     |           |
| Vitamin D  | Culture positive          | 15.21 (6.66)   | 0.334   | 14.5(7.7)         | 0.766     |
|            | Culture negative          | 13.87(6.97)    |         | 14.0(7.1)         |           |

**Table 3: Mean CRP, Ferritin, Vitamin- D levels in sepsis with shock and sepsis without shock group**

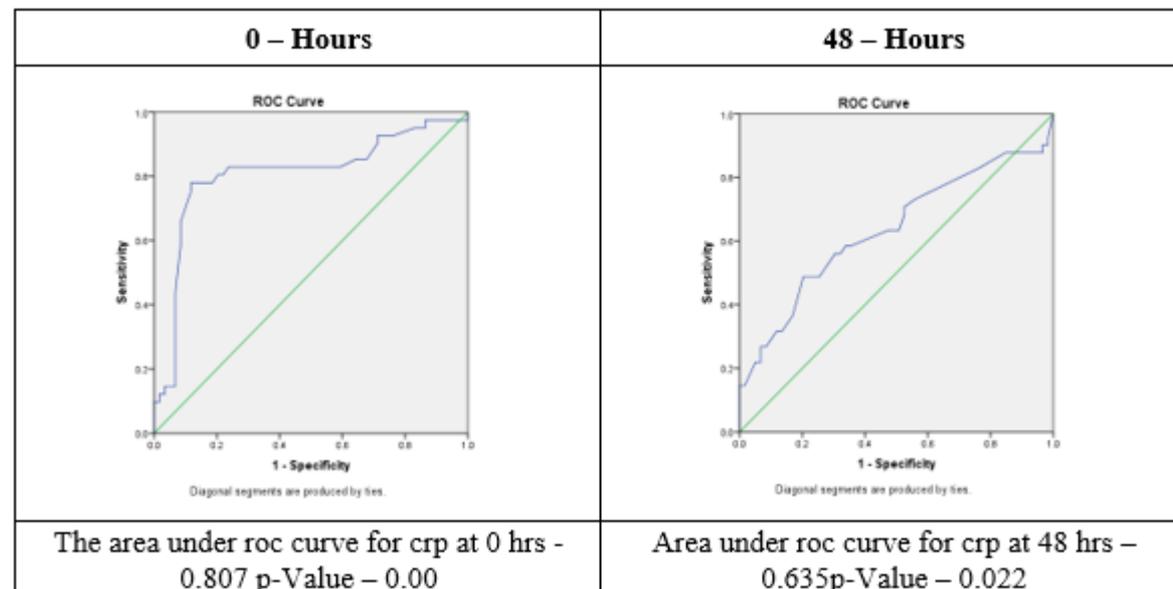
| Parameter        | Sepsis with or without shock | 0 hrs Mean (SD) | P-value | 48hs mean (SD) | p-value |
|------------------|------------------------------|-----------------|---------|----------------|---------|
| CRP (mg/l)       | Sepsis with shock            | 80.47(14.05)    | 0.00    | 39.16(21.0)    | 0.00    |
|                  | Sepsis without shock         | 46.34(25.69)    |         | 22.78(14.8)    |         |
| Ferritin (ng/ml) | Sepsis with shock            | 1418.4(282.0)   | 0.00    | 1539.4(1492.9) | 0.004   |
|                  | Sepsis without shock         | 385.4(333.5)    |         | 490.9(327.5)   |         |
| Vit-D level      | Sepsis with shock            | 14.08(6.79)     | 0.748   | 11.9(7.1)      | 0.043   |
|                  | Sepsis without shock         | 14.56(6.91)     |         | 15.2(7.1)      |         |

**Table 4: Comparison of diagnostic accuracy between CRP, Ferritin and Vitamin D**

| Parameter           | Sensitivity | Specificity | PPV   | NPV   | P-Value | AUC  | p-value | Correlation coefficient            |
|---------------------|-------------|-------------|-------|-------|---------|------|---------|------------------------------------|
| CRP >40mg/l         | 82.9%       | 45.8%       | 51.5% | 79.4% | 0.003   | 0.80 | 0.000   | With ferritin at 0 hrs r =0.46     |
| Ferritin > 200ng/ml | 82.9%       | 44.1%       | 50.7% | 78.8% | 0.005   | 0.72 | 0.002   | With CRP at 48 hrs r =0.308        |
| Vitamin D <15 ng/dl | 43.9%       | 37.3%       | 41.0% | 59.1% | 0.992   | 0.56 | 0.290   | With ferritin at 48 hrs r = -0.047 |



**Figure 1: Distribution of study group according to the sepsis criteria**



**Figure 2: ROC curves for CRP levels at 0hrs and 48hrs of admission**

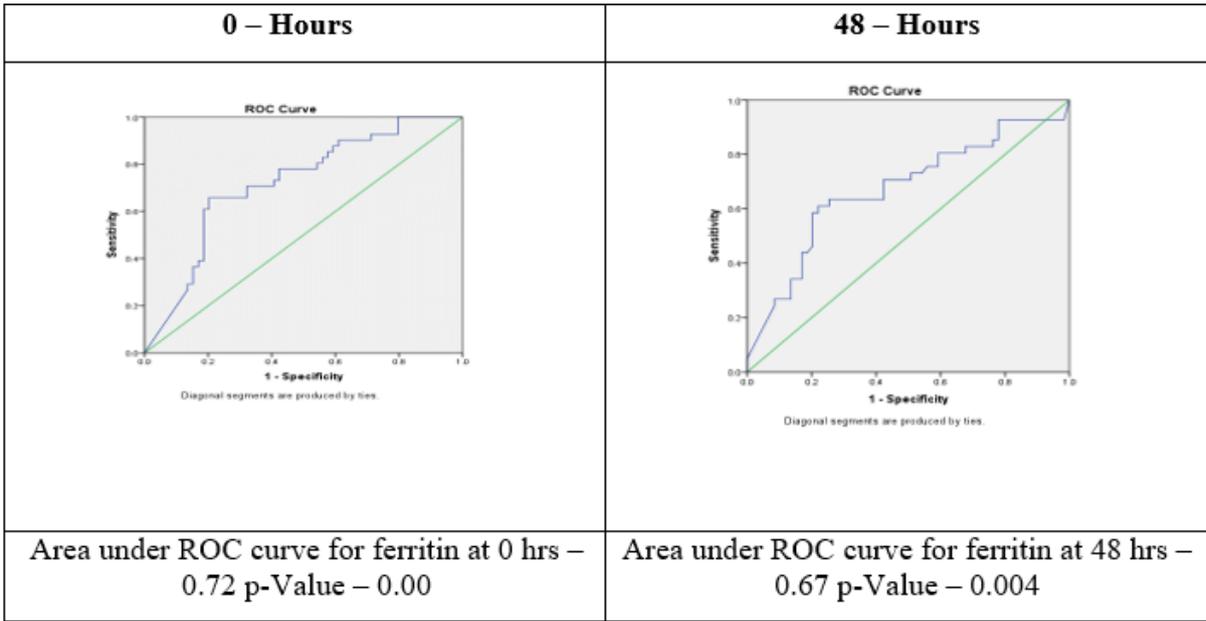


Figure 3: ROC curves for Ferritin levels at 0hrs and 48hrs of admission

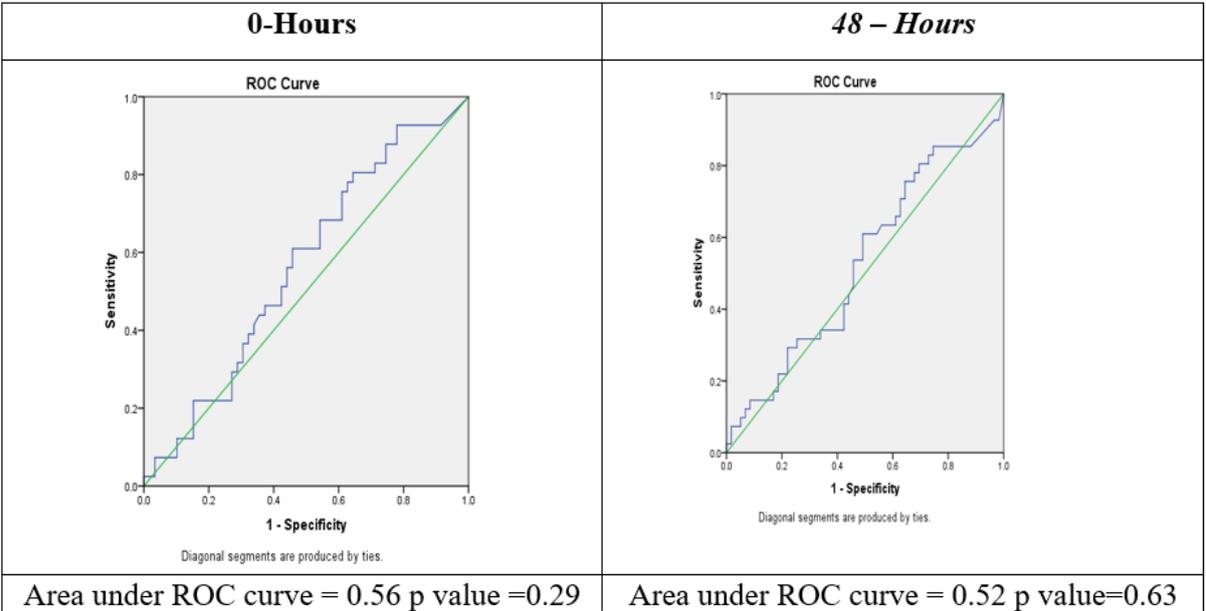


Figure 4: ROC curves for Vitamin D levels at 0hrs and 48hrs of admission

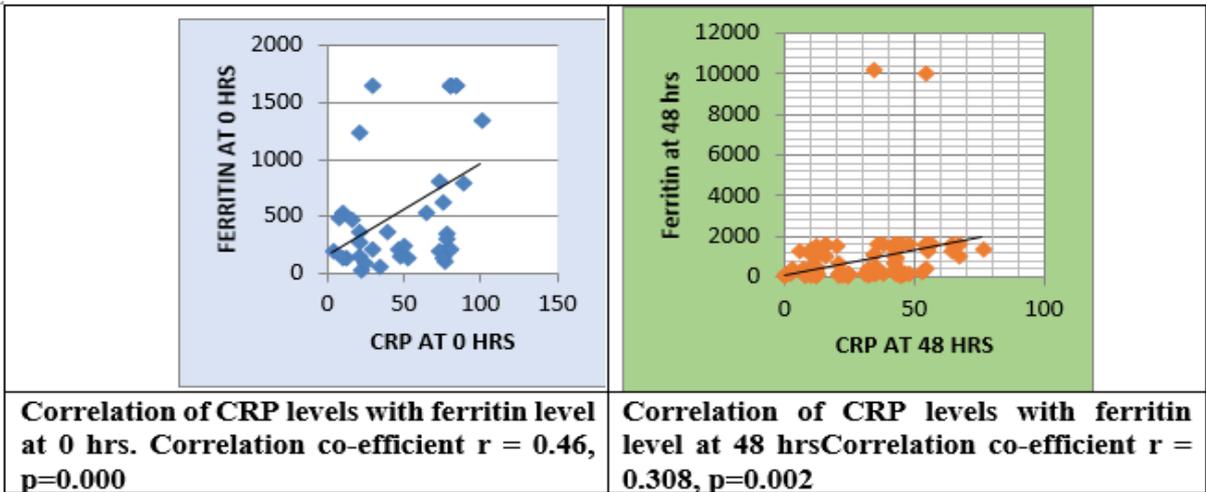


Figure 5: Pearson Correlation of CRP and Ferritin levels at 0 and 48 hrs.

Diagnostic accuracy of crp, ferritin and vitamin D. CRP at cutoff value more than 40 mg/l showed sensitivity of 82.9%, specificity of 45.8, PPV of 51.5% and NPV % with significant P value of 0.003. Area under the curve is greater for CRP at 0 hrs. than at 48 hrs. Ferritin levels at cut off value of 200ng/ml had sensitivity of 82.9% and specificity of 44.1%, PPV of 50.7% and NPV of 78.8%. The sensitivity and specificity of vitamin D with cut off value of 15ng/ml has sensitivity of 43.9% and specificity 37%. [Table 4]

Area under roc curve for crp at 0 hrs -0.807 p-Value – 0.00 and at 48 hrs – 0.635 p-Value – 0.022. [Figure 2]

ROC curve obtained for ferritin levels at 0 hrs and at 48 hrs with area under curve is more at 0 hrs (0.72, p value 0.00) and at 48hrs it is (0.67, p value0.004). [Figure 3]

ROC analysis with area under curve more in vitamin D levels at 0 hrs compared to 48hrs (AUC 0.56 p value-0.29 and 0.52, P value-0.63) respectively. [Figure 4]

In this analysis, there was positive correlation between CRP and ferritin at 0 hrs and 48 hrs. A negative correlation at 0 hrs and weak correlation between CRP and vitamin D at 48 hrs respectively was observed in this study as shown in figure 5. There was a weak correlation between ferritin and vitamin D at 0 hrs and negative correlation between ferritin and vit D at 48 hrs. [Figure 5]

## DISCUSSION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The mortality rate of sepsis in children from pediatric intensive care unit (PICU) of developing countries is higher than 50%.8. According to WHO global epidemiology report 2020, in India incidence of sepsis is 640 to <1600 per 100000 population and death due to sepsis was 25 to 30%. Globally 60 to 75% of the deaths of age group 1 to 14 yrs were due to infections, sepsis due to injuries in 10 to 20% and sepsis due to non-communicable diseases in 25% to 35% respectively. Several inflammatory indicators have been evaluated for early diagnosis of sepsis in various studies .The results of this study revealed potential benefits of determining inflammatory markers like C reactive protein (CRP), ferritin and Vitamin D in patients with sepsis that was culture negative clinically suspected(59%) or culture proven (41%) without shock and with shock. The mean length of stay in hospital for sepsis without shock patients were 7.57 days whereas the mean length of stay in hospital for sepsis with shock patients were 12.48 days.

In our study the sensitivity and specificity of CRP with cutoff value >40mg/l is 82.9% and 45.8% respectively. Suprin et al,<sup>[10]</sup> had demonstrated sensitivity 92% and specificity of 42%. In a study taken up by Kumar et al,<sup>[11]</sup> with 104 cases CRP

sensitivity of 72.22 % and specificity of 57.35%. Lacour et al,<sup>[12]</sup> study showed with CRP cut off value >40mg/l reported sensitivity of 89% and specificity of 76%.

ROC curve for ferritin levels at 0 hrs and at 48 hrs with area under curve didnt show significant difference. In this study Ferritin levels at cut off value of 200ng/ml had sensitivity of 82.9% and specificity of 44.1%, PPV of 50.7% and NPV of 78.8%. When ROC values between Crp and Ferritin were evaluated crp levels at 0 hrs and ferritin levels at 48 hrs had significant area under curve values. Garcia et al,<sup>[13]</sup> in their study two cut off values were taken 200ng /ml and 500ng/ml. The first cutoff, 200 ng/mL, was used because it is the upper limit of ferritin reported in inflammatory conditions. The second cutoff value, 500 ng/mL, was derived from levels reported in critically ill adults. In medical patients with ICU stay longer than 4 days ferritin level was 471 ng/mL. In a study done by Tellen D. Bennett et al,<sup>[14]</sup> Retrospective cohort study, open population.

Children with the highest ferritin levels ( $\geq 3000$  ng/mL) had a risk of dying four times as great and a risk of requiring intensive care 2.5 times as great as children with elevated, but lower ferritin levels (1000–3000 ng/mL). Children with ferritin level of >500 ng/mL) have long hospital lengths of stay. In this study the mean length of stay in hospital for sepsis without shock patients were 7.57 days whereas the mean length of stay in hospital for sepsis with shock patients were 12.48 days.<sup>[14]</sup>

In this study vitamin D deficiency ( $\leq 15$ ng/ml) is present in 61% of the patients. The mean vitamin D values in sepsis with shock and sepsis without shock and culture positive and culture negative patients at 0 hrs and 48 hrs is insignificant with p- value >0.05. The sensitivity and specificity with cut off value of 15ng/ml has sensitivity of 43.9% and specificity 37.3%. In a prospective study done by Constance Rippel et al in 2012 which included 316 patients found that.<sup>[15,16]</sup> There was no relationship between, length of stay, need for respiratory support, vasopressor support, and the need for, or duration of, vasoactive drug therapy between vitamin D deficient and without vitamin D deficiency in the postop cardiac group compared to general patients .There was no association between vitamin D status and actual or predicted (PIM2) mortality with p values >0.05. Even in the general medical group of patients they didn't find any significance in terms of hospital stay, intubation, respiratory support, vasopressor support, mortality rates between deficient groups and normal vitamin D groups with p values being >0.0523. ROC analysis with area under curve was more in vitamin D levels at 0 hrs compared to 48hrs (AUC 0.56 p value-0.29 and 0.52, P value-0.63) respectively. The diagnostic accuracy of Vitamin D is poor.

## CONCLUSION

This study revealed that CRP and Ferritin are good and early indicators of sepsis having equal sensitivity and specificity. Ferritin at 48 hrs has good prediction that longer hospital stay is required for sepsis to resolve. Vitamin D showed less diagnostic accuracy in this study. Limitations of this study are Outcome in terms of mortality was not included in this study and Control subjects were not taken to study vitamin D levels.

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